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(54) Title: COMBINATION COMPOSITION OF CHOLESTEROL ABSORPTION INHIBITOR AND 3-HYDROXY-3-METHYLGLUTARYL-COENZYME A (HMG-COA) REDUCTASE INHIBITOR

(57) Abstract: The present invention relates to stable antihyperlipoproteinemic combination of solid oral pharmaceutical formulations ezetimibe, HMG-CoA reductase inhibitor, disintegrants and glidants. For example, stable antihyperlipoproteinemic combination of solid oral pharmaceutical formulations, which comprises ezetimibe, simvastatin, starlac, ethanol, butylated hydroxy anisole, magnesium stearate, crospovidone, croscarmellose sodium, hydroxypropylcellulose (low-substituted), purified talc, lake brilliant blue, colloidal anhydrous silica, hydroxypropylmethylcellulose-15cps, titanium dioxide and triacetin.



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**COMBINATION COMPOSITION OF CHOLESTEROL ABSORPTION
INHIBITOR AND 3-HYDROXY-3-METHYLGUTARYL-COENZYME A (HMG-
COA) REDUCTASE INHIBITOR**

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FIELD OF THE INVENTION

The present invention relates to stable pharmaceutical compositions of antihyperlipoproteinemic drugs.

BACKGROUND OF THE INVENTION

Ezetimibe, chemically, (3R,4S)-1-(4-fluorophenyl)-3-[3(S)-3-(4-
10 fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone. Ezetimibe is a cholesterol absorption inhibitor. The therapeutic uses of ezetimibe and related compounds, and their preparations were disclosed in U.S. patent No. 5,767,115.

Ezetimibe is commercially available as 10 mg tablets. It is sold under
15 the name ZETIA.

Simvastatin, chemically, 2,2-dimethylbutanoic acid (1S,3R,7S,8S,8aR)-
1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-(tetrahydro-4-hydroxy-6-
oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester. Simvastatin is a 3-hydroxy-3-
methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor. The therapeutic
20 uses of simvastatin and related compounds, and their preparations were disclosed in U.S. patent No. 4,444,784.

Simvastatin is commercially available as 5 mg, 10 mg, 20 mg, 40 mg
and 80 mg tablets. It is sold under the name ZOCOR.

Atorvastatin, chemically, (β R, δ R)-2-(4-fluorophenyl)- β , δ -dihydroxy-5-
25 (1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid. Atorvastatin is a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor. The therapeutic uses of atorvastatin and related compounds, and their preparations were disclosed in U.S. patent No. 5,273,995.

Atorvastatin is commercially available as 10 mg, 20 mg, 40 mg and 80
30 mg tablets. It is sold under the name LIPITOR.

Rosuvastatin, chemically, [3R-[3R*,5S*(E)]]-7-[4-(4-fluorophenyl)-6-(1-
methylethyl)-2-[methyl(methylsulfonyl)amino]-5-pyrimidinyl]-3,5-dihydroxy-6-
heptenoic acid. Rosuvastatin is a HMG-CoA reductase inhibitor. The

therapeutic uses of rosuvastatin and related compounds, and their preparations were disclosed in U.S. patent No. 5,260,440.

Rosuvastatin is commercially available as 5 mg, 10 mg, 20 mg and 40 mg tablets. It is sold under the name CRESTOR.

5 The object of the present invention is to provide stable solid oral pharmaceutical compositions of antihyperlipoproteinemic drugs.

DETAILED DESCRIPTION OF THE INVENTION

10 The present invention relates to a stable antihyperlipoproteinemic combination of solid oral pharmaceutical compositions comprising ezetimibe, HMG-CoA reductase inhibitor, disintegrants and glidants.

15 According to the present invention, a stable antihyperlipoproteinemic combination of solid oral pharmaceutical formulations, which comprises ezetimibe, an HMG-CoA reductase inhibitor, disintegrants selected from starch, croscarmellose sodium and crospovidone, glidants selected from colloidal anhydrous silica and magnesium stearate. Other additives conventionally used for pharmaceutical formulations may be included in the present formulation.

20 The preferable HMG-CoA reductase inhibitors are simvastatin, atorvastatin and rosuvastatin; or a salt thereof.

25 The particularly preferable stable antihyperlipoproteinemic combination of solid oral pharmaceutical formulations, which comprises ezetimibe in the range of 1 to 15% by weight, more preferably 1.5 to 11% by weight; the HMG-CoA reductase inhibitor selected from simvastatin in the range of 1 to 25% by weight, more preferably 2 to 20% by weight; atorvastatin or a salt thereof in the range of 1 to 30% by weight, more preferably 2 to 25% by weight equivalent to atorvastatin and rosuvastatin or a salt thereof in the range of 2 to 12% by weight, more preferably 4 to 10% by weight equivalent to rosuvastatin; starch in the range of 2 to 25% by weight, more preferably 3 to 20% by weight; 30 croscarmellose sodium in the range of 1 to 8% by weight, more preferably 1.5 to 6.5% by weight; crospovidone in the range of 1 to 8% by weight, more preferably 1.5 to 6.5% by weight; colloidal anhydrous silica in the range of 0.1 to 2.5% by weight, more preferably 0.5 to 2% by weight and magnesium

stearate in the range of 0.5 to 5% by weight, more preferably 1 to 4% by weight, based on the total weight of the pharmaceutical dosage unit.

A stable antihyperlipoproteinemic combination of solid oral pharmaceutical formulations according to the invention comprises additives, which are conventionally used in dosage forms. These include but are not limited to disintegrants, binders, lubricants, glidants, fillers or diluents, stabilizing agents and the like.

As disintegrants one can particularly mention sodium starch glycolate, starch, croscarmellose sodium, crospovidone, carboxymethylcellulose calcium, carboxymethylcellulose sodium, magnesium aluminum silicate or a mixture thereof. As binders one can particularly mention starch, hydroxypropylcellulose, polyvinylpyrrolidone k-30, hydroxypropylcellulose (low-substituted); or a mixture thereof. As lubricants one can particularly mention stearic acid, pharmaceutically acceptable derivatives of stearic acid, talc, sodium stearyl fumarate, glyceryl behenate, magnesium silicate, magnesium trisilicate, hydrogenated castor oil; or a mixture thereof. As glidants one can particularly mention colloidal anhydrous silica, talc or a mixture thereof. As preservatives one can particularly mention butylated hydroxy anisole, butylated hydroxy toluene, methyl paraben, propyl paraben; or a mixture thereof. As fillers one can particularly mention calcium carbonate, dibasic calcium phosphate, lactose, magnesium carbonate, sucrose, starch, magnesium oxide, lactose anhydrous, microcrystalline cellulose, mannitol; or a mixture thereof. Other ingredients such as coating materials, anti-adherents, plasticizer, colorants, opacifiers, antioxidants and solvents conventionally used for pharmaceutical formulations.

The pharmaceutical composition may be for example, in the form of a tablet, a caplet, pellets, a capsule, granules, a pill, powder or a sachet. Preferably the pharmaceutical composition is in the form of a combination antihyperlipoproteinemic tablet. Stable mixture, which is highly compressible, have good flow properties, thereby providing the tablets with excellent physical properties. The pharmaceutical composition of the present invention is administered orally.

An improved stable antihyperlipoproteinemic combination of solid oral pharmaceutical formulations, which comprises ezetimibe, simvastatin, starlac,

ethanol, butylated hydroxy anisole, magnesium stearate, crospovidone, croscarmellose sodium, hydroxypropylcellulose (low-substituted), purified talc, lake brilliant blue, colloidal anhydrous silica, hydroxypropylmethylcellulose-15cps, titanium dioxide and triacetin.

5 The present invention provides a formulation suitable for forming ezetimibe and simvastatin combination tablets comprising ezetimibe in the range of 1 to 10% by weight, more preferably 1.5 to 7.5% by weight, simvastatin in the range of 2 to 23% by weight, more preferably 3 to 18% by weight, starlac in the range of 41 to 97% by weight, more preferably 61 to 87%
10 by weight, butylated hydroxy anisole in the range of 0.01 to 0.004% by weight, more preferably 0.01 to 0.03% by weight, magnesium stearate in the range of 1 to 3% by weight, more preferably 1.5 to 2.5% by weight, crospovidone in the range of 1 to 6% by weight, more preferably 1.5 to 5% by weight, croscarmellose sodium in the range of 1 to 4% by weight, more preferably 1.5
15 to 3% by weight, hydroxypropylcellulose (low-substituted) in the range of 2 to 7% by weight, more preferably 2.5 to 6.5% by weight, colloidal anhydrous silica in the range of 0.5 to 2% by weight, more preferably 0.5 to 1.5% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps in the range of 37 to 89.5% by weight, more preferably 56 to 70% by
20 weight, purified talc in the range of 4 to 12% by weight, more preferably 7 to 9.5% by weight, lake brilliant blue in the range of 4 to 14% by weight, more preferably 9 to 11% by weight, titanium dioxide in the range of 7 to 18% by weight, more preferably 11 to 14.5% by weight and triacetin in the range of 3 to 9% by weight, more preferably 5 to 6.5% by weight, based on the total
25 weight of the coating material. Optionally additional excipients may be used. In addition to the active ingredient, solid dosage forms contain a number of additional additives used in single dosage units.

The particularly preferable tablet formulations are:

i) Ezetimibe (10mg) and simvastatin (5mg); which comprises ezetimibe is
30 6.7% by weight, simvastatin is 3.3% by weight, starlac is 77.3% by weight, butylated hydroxy anisole is 0.02% by weight, magnesium stearate is 1.7% by weight, crospovidone is 2.7% by weight, croscarmellose sodium is 2% by weight, hydroxypropylcellulose (low-substituted) is 5.3% by weight, colloidal anhydrous silica is 1% by weight, based on the total weight of the tablet,

hydroxypropylmethylcellulose-15cps is 63.7% by weight, purified talc is 8% by weight, lake brilliant blue is 10% by weight, titanium dioxide is 12.7% by weight and triacetin is 5.7% by weight, based on the total weight of the coating material.

5 ii) Ezetimibe (10mg) and simvastatin (10mg); which comprises ezetimibe is 5.6% by weight, simvastatin is 5.6% by weight, starlac is 79.4% by weight, butylated hydroxy anisole is 0.02% by weight, magnesium stearate is 1.7% by weight, crospovidone is 2.2% by weight, croscarmellose sodium is 1.7% by weight, hydroxypropylcellulose (low-substituted) is 2.8% by weight, colloidal
10 anhydrous silica is 1.1% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps is 63.6% by weight, purified talc is 8.1% by weight, lake brilliant blue is 10% by weight, titanium dioxide is 12.8% by weight and triacetin is 5.6% by weight, based on the total weight of the coating material.

15 iii) Ezetimibe (10mg) and simvastatin (20mg); which comprises ezetimibe is 3.3% by weight, simvastatin is 6.7% by weight, starlac is 78.1% by weight, butylated hydroxy anisole is 0.03% by weight, magnesium stearate is 1.7% by weight, crospovidone is 2% by weight, croscarmellose sodium is 1.7% by weight, hydroxypropylcellulose (low-substituted) is 5.7% by weight, colloidal
20 anhydrous silica is 0.8% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps is 63.5% by weight, purified talc is 8.2% by weight, lake brilliant blue is 10% by weight, titanium dioxide is 12.7% by weight and triacetin is 5.7% by weight, based on the total weight of the coating material.

25 iv) Ezetimibe (10mg) and simvastatin (40mg); which comprises ezetimibe is 2.6% by weight, simvastatin is 10.3% by weight, starlac is 75.1% by weight, butylated hydroxy anisole is 0.02% by weight, magnesium stearate is 2.1% by weight, crospovidone is 2.1% by weight, croscarmellose sodium is 1.8% by weight, hydroxypropylcellulose (low-substituted) is 5.1% by weight, colloidal
30 anhydrous silica is 1% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps is 63.2% by weight, purified talc is 8.2% by weight, lake brilliant blue is 10% by weight, titanium dioxide is 12.8% by weight and triacetin is 2.3% by weight, based on the total weight of the coating material.

v) Ezetimibe (10mg) and simvastatin (80mg); which comprises ezetimibe is 2% by weight, simvastatin is 16% by weight, starlac is 67.8% by weight, butylated hydroxy anisole is 0.02% by weight, magnesium stearate is 2% by weight, crospovidone is 4% by weight, croscarmellose sodium is 2.6% by weight, hydroxypropylcellulose (low-substituted) is 4.6% by weight, colloidal anhydrous silica is 1% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps is 63.3% by weight, purified talc is 8.1% by weight, lake brilliant blue is 10% by weight, titanium dioxide is 12.8% by weight and triacetin is 5.8% by weight, based on the total weight of the coating material.

An improved stable antihyperlipoproteinemic combination of solid oral pharmaceutical formulations, which comprises ezetimibe, atorvastatin and rosuvastatin or a salt thereof, light calcium carbonate, lactose, starch, croscarmellose sodium, polyvinylpyrrolidone k-30, isopropyl alcohol, titanium dioxide, magnesium stearate, colloidal anhydrous silica, crospovidone, hydroxypropylmethylcellulose-15cps, purified talc, lake sunset yellow and triacetin.

The present invention provides a formulation suitable for forming ezetimibe and atorvastatin; or a salt thereof combination tablets comprising ezetimibe in the range of 1.5 to 13% by weight, more preferably 2 to 10% by weight, atorvastatin; or a salt thereof in the range of 3 to 31% by weight, more preferably 4 to 24% by weight equivalent to atorvastatin, light calcium carbonate in the range of 2 to 8% by weight, more preferably 3 to 6.5% by weight, lactose in the range of 27 to 80% by weight, more preferably 40 to 63% by weight, starch in the range of 5 to 24% by weight, more preferably 8 to 19% by weight, croscarmellose sodium in the range of 2 to 8% by weight, more preferably 3 to 6% by weight, polyvinylpyrrolidone k-30 in the range of 1 to 7% by weight, more preferably 2.5 to 6% by weight, magnesium stearate in the range of 1 to 4% by weight, more preferably 1.5 to 3% by weight, colloidal anhydrous silica in the range of 0.5 to 2.5% by weight, more preferably 0.5 to 2% by weight, crospovidone in the range of 1.5 to 6% by weight, more preferably 2 to 4.5% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps in the range of 50 to 90% by weight, more preferably 65 to 80% by weight, purified talc in the range of 5 to

10% by weight, more preferably 7 to 9% by weight, lake sunset yellow in the range of 0.5 to 2% by weight, more preferably 1 to 1.5% by weight, titanium dioxide in the range of 8.5 to 18% by weight, more preferably 11 to 14.5% by weight and triacetin in the range of 4 to 8% by weight, more preferably 5 to 7%
5 by weight, based on the total weight of the coating material. Optionally additional excipients may be used. In addition to the active ingredient, solid dosage forms contain a number of additional additives used in single dosage units.

The particularly preferable tablet formulations are:

10 i) Ezetimibe (10mg) and atorvastatin (5mg); which comprises ezetimibe is 9.09% by weight, atorvastatin or a salt thereof is 4.92% by weight equivalent to atorvastatin, light calcium carbonate is 3.64% by weight, lactose is 51.4% by weight, starch is 17.3% by weight, croscarmellose sodium is 3.62% by weight, polyvinylpyrrolidone k-30 is 4.09% by weight, magnesium stearate is
15 1.82% by weight, colloidal anhydrous silica is 1.36% by weight, crospovidone is 2.73% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps is 72.3% by weight, purified talc is 7.73% by weight, lake sunset yellow is 1.36% by weight, titanium dioxide is 12.7% by weight and triacetin is 5.91% by weight, based on the total weight of
20 the coating material.

ii) Ezetimibe (10mg) and atorvastatin (10mg); which comprises ezetimibe is 6.7% by weight, atorvastatin or a salt thereof is 7.2% by weight equivalent to atorvastatin, light calcium carbonate is 4.7% by weight, lactose is 56.8% by weight, starch is 10.7% by weight, croscarmellose sodium is 3.4% by weight,
25 polyvinylpyrrolidone k-30 is 5% by weight, magnesium stearate is 2% by weight, colloidal anhydrous silica is 1% by weight, crospovidone is 2.7% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps is 72.3% by weight, purified talc is 8% by weight, lake sunset yellow is 1.33% by weight, titanium dioxide is 12.7% by weight and triacetin is 5.7% by
30 weight, based on the total weight of the coating material.

iii) Ezetimibe (10mg) and atorvastatin (20mg); which comprises ezetimibe is 5.56% by weight, atorvastatin or a salt thereof is 12% by weight equivalent to atorvastatin, light calcium carbonate is 5.56% by weight, lactose is 51.3% by weight, starch is 8.89% by weight, croscarmellose sodium is 4.6% by weight,

polyvinylpyrrolidone k-30 is 3.33% by weight, magnesium stearate is 2.22% by weight, colloidal anhydrous silica is 1.7% by weight, crospovidone is 3.9% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps is 72.2% by weight, purified talc is 8.06% by weight, lake sunset yellow is 1.39% by weight, titanium dioxide is 12.8% by weight and triacetin is 5.56% by weight, based on the total weight of the coating material.

iv) Ezetimibe (10mg) and atorvastatin (40mg); which comprises ezetimibe is 3.3% by weight, atorvastatin or a salt thereof is 14.4% by weight equivalent to atorvastatin, light calcium carbonate is 5% by weight, lactose is 50.3% by weight, starch is 11.7% by weight, croscarmellose sodium is 4.4% by weight, polyvinylpyrrolidone k-30 is 2.8% by weight, magnesium stearate is 2.7% by weight, colloidal anhydrous silica 1.3% by weight, crospovidone is 4% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps is 71.83% by weight, purified talc is 8.17% by weight, lake sunset yellow is 1.33% by weight, titanium dioxide is 12.8% by weight and triacetin is 5.83% by weight, based on the total weight of the coating material.

v) Ezetimibe (10mg) and atorvastatin (80mg); which comprises ezetimibe is 2.56% by weight, atorvastatin or a salt thereof is 22.2% by weight equivalent to atorvastatin, light calcium carbonate is 5.13% by weight, lactose is 44.9% by weight, starch is 10.3% by weight, croscarmellose sodium is 4.6% by weight, polyvinylpyrrolidone k-30 is 2.82% by weight, magnesium stearate is 2.31% by weight, colloidal anhydrous silica is 1.3% by weight, crospovidone is 3.9% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps is 71.8% by weight, purified talc is 8.21% by weight, lake sunset yellow is 1.41% by weight, titanium dioxide is 12.8% by weight and triacetin is 5.77% by weight, based on the total weight of the coating material.

The present invention provides a formulation suitable for forming ezetimibe and rosuvastatin or a salt thereof combination tablets comprising ezetimibe in the range of 2 to 13% by weight, more preferably 3 to 10% by weight, rosuvastatin; or a salt thereof in the range of 2 to 10.5% by weight, more preferably 4 to 8.5% by weight equivalent to rosuvastatin, light calcium carbonate in the range of 1 to 4% by weight, more preferably 1.5 to 3% by weight, lactose in the range of 32 to 83% by weight, more preferably 49 to

65% by weight, starch in the range of 8 to 21% by weight, more preferably 12 to 16.5% by weight, croscarmellose sodium in the range of 2 to 6.5% by weight, more preferably 2.5 to 5% by weight, polyvinylpyrrolidone k-30 in the range of 1 to 5% by weight, more preferably 2 to 3.5% by weight, magnesium stearate in the range of 1 to 3.5% by weight, more preferably 1.5 to 3% by weight, colloidal anhydrous silica in the range of 0.5 to 2% by weight, more preferably 0.5 to 1.5% by weight, crospovidone in the range of 2 to 7% by weight, more preferably 4 to 5.5% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps in the range of 52 to 93% by weight, more preferably 65 to 80% by weight, purified talc in the range of 5 to 10% by weight, more preferably 7 to 9% by weight, lake sunset yellow in the range of 0.5 to 2.5% by weight, more preferably 1 to 2% by weight, titanium dioxide in the range of 8 to 16% by weight, more preferably 11 to 14% by weight and triacetin in the range of 4 to 8% by weight, more preferably 5 to 6.5% by weight, based on the total weight of the coating material. Optionally additional excipients may be used. In addition to the active ingredient, solid dosage forms contain a number of additional additives used in single dosage units.

The particularly preferable tablet formulations are:

- i) Ezetimibe (10mg) and rosuvastatin (5mg); which comprises ezetimibe is 9.09% by weight, rosuvastatin or a salt thereof is 4.74% by weight equivalent to rosuvastatin, light calcium carbonate is 2.3% by weight, lactose is 54.5% by weight, starch is 13.9% by weight, croscarmellose sodium is 4.6% by weight, polyvinylpyrrolidone k-30 is 3.2% by weight, magnesium stearate is 1.8% by weight, colloidal anhydrous silica is 0.9% by weight, crospovidone is 5% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps is 71.8% by weight, purified talc is 8.2% by weight, lake sunset yellow is 1.4% by weight, titanium dioxide is 12.7% by weight and triacetin is 5.9% by weight, based on the total weight of the coating material.
- ii) Ezetimibe (10mg) and rosuvastatin (10mg); which comprises ezetimibe is 5.7% by weight, rosuvastatin or a salt thereof is 5.95% by weight equivalent to rosuvastatin, light calcium carbonate is 2.3% by weight, lactose is 57.5% by weight, starch is 13.7% by weight, croscarmellose sodium is 4% by weight, polyvinylpyrrolidone k-30 is 2.9% by weight, magnesium stearate is 2.3% by

weight, colloidal anhydrous silica is 1.1% by weight, crospovidone is 4.6% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps is 72.3% by weight, purified talc is 8% by weight, lake sunset yellow is 1.43% by weight, titanium dioxide is 12.6% by weight and triacetin is 5.7% by weight, based on the total weight of the coating material.

iii) Ezetimibe (10mg) and rosuvastatin (20mg); which comprises ezetimibe is 3.6% by weight, rosuvastatin or a salt thereof is 7.4% by weight equivalent to rosuvastatin, light calcium carbonate is 2.1% by weight, lactose is 58.8% by weight, starch is 14.8% by weight, croscarmellose sodium is 3.2% by weight, polyvinylpyrrolidone k-30 is 2.3% by weight, magnesium stearate is 1.8% by weight, colloidal anhydrous silica is 0.9% by weight, crospovidone is 5% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps is 72.1% by weight, purified talc is 8.04% by weight, lake sunset yellow is 1.43% by weight, titanium dioxide is 12.7% by weight and triacetin is 5.7% by weight, based on the total weight of the coating material.

The invention is explained in detail in the examples given below which are provided by the way of illustration only and therefore should not be construed to limit the scope of the invention.

EXAMPLES

In the following embodiments of the invention, the below listed quantities of drug substances and additional components are combined using standard pharmaceutical manufacturing techniques. The resulting formulations are used to compress into tablets.

Tablet formulation:

Method of manufacture: The ezetimibe, simvastatin and starlac are granulated using binder solution of butylated hydroxy anisole and ethanol in planetary mixer, rapid mixer granulator; or other suitable granulator. This wet mass may be then dried. The dried granulation may be then milled to achieve the desired particle size distribution and then blended with the other ingredients. This blend is compressed into tablets. These compressed tablets are coated using a non aqueous solution of hydroxypropylmethylcellulose-15cps, purified talc, lake brilliant blue, titanium dioxide and triacetin by using autocota, neocota; or other suitable coating pan.

Example 1

The components and their amounts were as follows:

Ezetimibe (10mg) and simvastatin (5mg) tablets:

	Ingredients	Quantity (mg)	%(W/W)
5	Ezetimibe	10	6.7
	Simvastatin	5	3.3
	Starlac	59	39.3
	Ethanol	q.s	-
	Butylated hydroxy anisole	0.03	0.02
10	Starlac	56.97	38
	Magnesium stearate	2.5	1.7
	Crospovidone	4	2.7
	Croscarmellose sodium	3	2
	L-hydroxypropylcellulose (LH-11)	8	5.3
15	Colloidal anhydrous silica	1.5	1
	Tablet weight	150	-
	Hydroxypropylmethylcellulose-15cps	1.91	63.7
	Purified talc	0.24	8
	Lake brilliant blue	0.30	10
20	Titanium dioxide	0.38	12.7
	Triacetin	0.17	5.7

Example 2

The components and their amounts were as follows:

25 Ezetimibe (10mg) and simvastatin (10mg) tablets:

	Ingredients	Quantity (mg)	%(W/W)
	Ezetimibe	10	5.6
	Simvastatin	10	5.6
	Starlac	70	38.9
30	Ethanol	q.s	-
	Butylated hydroxy anisole	0.04	0.02
	Starlac	72.96	40.5
	Magnesium stearate	3	1.7

	Crospovidone	4	2.2
	Croscarmellose sodium	3	1.7
	L-hydroxypropylcellulose (LH-11)	5	2.8
	Colloidal anhydrous silica	2	1.1
5	Tablet weight	180	-
	Hydroxypropylmethylcellulose-15cps	2.29	63.6
	Purified talc	0.29	8.1
	Lake brilliant blue	0.36	10
	Titanium dioxide	0.46	12.8
10	Triacetin	0.2	5.6

Example 3

The components and their amounts were as follows:

Ezetimibe (10mg) and simvastatin (20mg) tablets:

15	Ingredients	Quantity (mg)	%(W/W)
	Ezetimibe	10	3.3
	Simvastatin	20	6.7
	Starlac	120.71	40.2
	Ethanol	q.s	-
20	Butylated hydroxy anisole	0.08	0.03
	Starlac	113.71	37.9
	Magnesium stearate	5	1.7
	Crospovidone	6	2
	Croscarmellose sodium	5	1.7
25	L-hydroxypropylcellulose (LH-11)	17	5.7
	Colloidal anhydrous silica	2.5	0.8
	Tablet weight	300	-
	Hydroxypropylmethylcellulose-15cps	3.81	63.5
	Purified talc	0.49	8.2
30	Lake brilliant blue	0.60	10
	Titanium dioxide	0.76	12.7
	Triacetin	0.34	5.7

Example 4

The components and their amounts were as follows:

Ezetimibe (10mg) and simvastatin (40mg) tablets:

	Ingredients	Quantity (mg)	%(W/W)
5	Ezetimibe	10	2.6
	Simvastatin	40	10.3
	Starlac	148	37.9
	Ethanol	q.s	-
	Butylated hydroxy anisole	0.09	0.02
10	Starlac	144.91	37.2
	Magnesium stearate	8	2.1
	Crospovidone	8	2.1
	Croscarmellose sodium	7	1.8
	L-hydroxypropylcellulose (LH-11)	20	5.11
15	Colloidal anhydrous silica	4	1
	Tablet weight	390	-
	Hydroxypropylmethylcellulose-15cps	4.93	63.2
	Purified talc	0.64	8.2
	Lake brilliant blue	0.78	10
20	Titanium dioxide	1	12.8
	Triacetin	0.45	5.8

Example 5

The components and their amounts were as follows:

25 Ezetimibe (10mg) and simvastatin (80mg) tablets:

	Ingredients	Quantity (mg)	%(W/W)
	Ezetimibe	10	2
	Simvastatin	80	16
	Starlac	173	34.6
30	Ethanol	q.s	-
	Butylated hydroxy anisole	0.1	0.02
	Starlac	165.9	33.2
	Magnesium stearate	10	2

	Crospovidone	20	4
	Croscarmellose sodium	13	2.6
	L-hydroxypropylcellulose (LH-11)	23	4.6
	Colloidal anhydrous silica	5	1
5	Tablet weight	500	-
	Hydroxypropylmethylcellulose-15cps	6.33	63.3
	Purified talc	0.81	8.1
	Lake brilliant blue	1.0	10
	Titanium dioxide	1.28	12.8
10	Triacetin	0.58	5.8

Method of manufacture: The ezetimibe, HMG-CoA reductase inhibitor, light calcium carbonate, lactose, starch and croscarmellose sodium are granulated using binder solution of polyvinylpyrrolidone k-30 and isopropyl alcohol in planetary mixer, rapid mixer granulator; or other suitable granulator.

- 15 This wet mass may be then dried. The dried granulation may be then milled to achieve the desired particle size distribution and then blended with the other ingredients. This blend is compressed into tablets. These compressed tablets are coated using a non aqueous solution of hydroxypropylmethylcellulose-15cps, purified talc, lake sunset yellow, titanium dioxide and triacetin by using
- 20 autocota, neocota; or other suitable coating pan.

Example 6

The components and their amounts were as follows:

Ezetimibe (10mg) and atorvastatin (5mg) tablets:

25	Ingredients	Quantity (mg)	%(W/W)
	Ezetimibe	10	9.09
	Atorvastatin calcium		
	Eq.to atorvastatin	5.415	4.92
	Light calcium carbonate	4	3.64
30	Lactose	56.585	51.4
	Starch	19	17.3
	Croscarmellose sodium	2	1.82
	Polyvinylpyrrolidone k-30	4.5	4.09
	Isopropyl alcohol	q.s	-

	Magnesium stearate	2	1.82
	Colloidal anhydrous silica	1.5	1.36
	Crospovidone	3	2.73
	Croscarmellose sodium	2	1.82
5	Tablet weight	110	-
	Hydroxypropylmethylcellulose-15cps	1.59	72.23
	Purified talc	0.17	7.73
	Lake sunset yellow	0.03	1.36
	Titanium dioxide	0.28	12.7
10	Triacetin	0.13	5.91

Example 7

The components and their amounts were as follows:

Ezetimibe (10mg) and atorvastatin (10mg) tablets:

15	Ingredients	Quantity (mg)	%(W/W)
	Ezetimibe	10	6.7
	Atorvastatin calcium		
	Eq.to atorvastatin	10.83	7.2
	Light calcium carbonate	7	4.7
20	Lactose	85.17	56.8
	Starch	16	10.7
	Croscarmellose sodium	2.5	1.7
	Polyvinylpyrrolidone k-30	7.5	5
	Isopropyl alcohol	q.s	-
25	Magnesium stearate	3	2
	Colloidal anhydrous silica	1.5	1
	Crospovidone	4	2.7
	Croscarmellose sodium	2.5	1.7
	Tablet weight	150	-
30	Hydroxypropylmethylcellulose-15cps	2.17	72.3
	Purified talc	0.24	8
	Lake sunset yellow	0.04	1.3
	Titanium dioxide	0.38	12.7
	Triacetin	0.17	5.7

Example 8

The components and their amounts were as follows:

Ezetimibe (10mg) and atorvastatin (20mg) tablets:

	Ingredients	Quantity (mg)	%(W/W)
5	Ezetimibe	10	5.56
	Atorvastatin calcium		
	Eq.to atorvastatin	21.66	12
	Light calcium carbonate	10	5.56
	Lactose	92.34	51.3
10	Starch	16	8.9
	Croscarmellose sodium	5	2.8
	Polyvinylpyrrolidone k-30	6	3.33
	Isopropyl alcohol	q.s	-
	Magnesium stearate	4	2.22
15	Colloidal anhydrous silica	3	1.7
	Crospovidone	7	3.9
	Croscarmellose sodium	5	2.8
	Tablet weight	180	-
	Hydroxypropylmethylcellulose-15cps	2.60	72.2
20	Purified talc	0.29	8.06
	Lake sunset yellow	0.05	1.39
	Titanium dioxide	0.46	12.8
	Triacetin	0.20	5.56

Example 9

The components and their amounts were as follows:

Ezetimibe (10mg) and atorvastatin (40mg) tablets:

	Ingredients	Quantity (mg)	%(W/W)
	Ezetimibe	10	3.3
30	Atorvastatin calcium		
	Eq.to atorvastatin	43.32	14.4
	Light calcium carbonate	15	5
	Lactose	151	50.3
	Starch	35.18	11.7

	Croscarmellose sodium	6.5	2.2
	Polyvinylpyrrolidone k-30	8.5	2.8
	Isopropyl alcohol	q.s	-
	Magnesium stearate	8	2.7
5	Colloidal anhydrous silica	4	1.3
	Crospovidone	12	4
	Croscarmellose sodium	6.5	2.2
	Tablet weight	300	-
	Hydroxypropylmethylcellulose-15cps	4.31	7.80
10	Purified talc	0.49	8.17
	Lake sunset yellow	0.08	1.33
	Titanium dioxide	0.77	12.8
	Triacetin	0.35	5.83

15 **Example 10**

The components and their amounts were as follows:

Ezetimibe (10mg) and atorvastatin (80mg) tablets:

	Ingredients	Quantity (mg)	%(W/W)
	Ezetimibe	10	2.56
20	Atorvastatin calcium		
	Eq.to atorvastatin	86.64	22.2
	Light calcium carbonate	20	5.13
	Lactose	175	44.9
	Starch	40.36	10.3
25	Croscarmellose sodium	9	2.3
	Polyvinylpyrrolidone k-30	11	2.82
	Isopropyl alcohol	q.s	-
	Magnesium stearate	9	2.3
	Colloidal anhydrous silica	5	1.3
30	Crospovidone	15	3.9
	Croscarmellose sodium	9	2.3
	Tablet weight	390	-
	Hydroxypropylmethylcellulose-15cps	5.60	71.8
	Purified talc	0.64	8.21

Lake sunset yellow	0.11	1.41
Titanium dioxide	1.0	12.8
Triacetin	0.45	5.77

5 Example 11

The components and their amounts were as follows:

Ezetimibe (10mg) and rosuvastatin (5mg) tablets:

Ingredients	Quantity (mg)	%(W/W)
Ezetimibe	10	9.09
10 Rosuvastatin calcium		
Eq.to rosuvastatin	5.21	4.74
Light calcium carbonate	2.5	2.3
Lactose anhydrous	60	54.5
Starch	15.29	13.9
15 Croscarmellose sodium	2.5	2.3
Polyvinylpyrrolidone k-30	3.5	3.2
Isopropyl alcohol	q.s	-
Magnesium stearate	2	1.8
Colloidal anhydrous silica	1	0.9
20 Crospovidone	5.5	5
Croscarmellose sodium	2.5	2.3
Tablet weight	110	-
Hydroxypropylmethylcellulose-15cps	1.58	71.8
Purified talc	0.18	8.2
25 Lake sunset yellow	0.03	1.4
Titanium dioxide	0.28	12.7
Triacetin	0.13	5.9

Example 12

30 The components and their amounts were as follows:

Ezetimibe (10mg) and rosuvastatin (10mg) tablets:

Ingredients	Quantity (mg)	%(W/W)
Ezetimibe	10	5.7
Rosuvastatin calcium		

	Eq.to rosuvastatin	10.42	5.95
	Light calcium carbonate	4	2.3
	Lactose anhydrous	100.58	57.5
	Starch	24	13.7
5	Croscarmellose sodium	3.5	2
	Polyvinylpyrrolidone k-30	5	2.9
	Isopropyl alcohol	q.s	-
	Magnesium stearate	4	2.3
	Colloidal anhydrous silica	2	1.14
10	Crospovidone	8	4.6
	Croscarmellose sodium	3.5	2
	Tablet weight	175	-
	Hydroxypropylmethylcellulose-15cps	2.53	72.3
	Purified talc	0.28	8
15	Lake sunset yellow	0.05	1.43
	Titanium dioxide	0.44	12.6
	Triacetin	0.20	5.7

Example 13

20 The components and their amounts were as follows:

Ezetimibe (10mg) and rosuvastatin (20mg) tablets:

	Ingredients	Quantity (mg)	%(W/W)
	Ezetimibe	10	3.6
	Rosuvastatin calcium		
25	Eq.to rosuvastatin	20.84	7.4
	Light calcium carbonate	6	2.1
	Lactose anhydrous	164.66	58.8
	Starch	41.5	14.8
	Croscarmellose sodium	4.5	1.6
30	Polyvinylpyrrolidone k-30	6.5	2.3
	Isopropyl alcohol	q.s	-
	Magnesium stearate	5	1.8
	Colloidal anhydrous silica	2.5	0.9
	Crospovidone	14	5

	Croscarmellose sodium	4.5	1.6
	Tablet weight	280	-
	Hydroxypropylmethylcellulose-15cps	4.04	72.1
	Purified talc	0.45	8.04
5	Lake sunset yellow	0.08	1.43
	Titanium dioxide	0.71	12.7
	Triacetin	0.32	5.7

10

15

We claim:

1. Antihyperlipoproteinemic combination of solid oral pharmaceutical formulations, which comprises ezetimibe, an HMG-CoA reductase inhibitor, disintegrants selected from starch, croscarmellose sodium and
5 crospovidone, glidants selected from colloidal anhydrous silica and magnesium stearate.
2. The formulation as claimed in claim 1, wherein HMG-CoA reductase inhibitors are simvastatin, atorvastatin, rosuvastatin and or a salt thereof.
3. The formulation as claimed in claim 2, wherein ezetimibe in the range of 1
10 to 15% by weight; the HMG-CoA reductase selected from inhibitor simvastatin in the range of 1 to 25% by weight; atorvastatin or a salt thereof in the range of 1 to 30% by weight and rosuvastatin or a salt thereof in the range of 2 to 12% by weight; starch in the range of 2 to 25%
15 by weight; croscarmellose sodium in the range of 1 to 8% by weight; crospovidone in the range of 1 to 8% by weight; colloidal anhydrous silica in the range of 0.1 to 2.5% by weight and magnesium stearate in the range of 0.5 to 5% by weight, based on the total weight of the pharmaceutical dosage unit.
4. The formulation as claimed in claim 3, wherein ezetimibe in the range of
20 1.5 to 11% by weight; the HMG-CoA reductase selected from inhibitor simvastatin in the range of 2 to 20% by weight; atorvastatin or a salt thereof in the range of 2 to 25% by weight equivalent to atorvastatin and rosuvastatin or a salt thereof in the range of 4 to 10% by weight equivalent to rosuvastatin; starch in the range of 3 to 20% by weight; croscarmellose
25 sodium in the range of by weight; crospovidone in the range of by weight; colloidal anhydrous silica in the range of 0.5 to 2% by weight and magnesium stearate in the range of 1 to 4% by weight, based on the total weight of the pharmaceutical dosage unit.
5. The formulation as claimed in claim 1, wherein the said formulation is in
30 the form of a tablet, a caplet, pellets, a capsule, granules, a pill, powder or a sachet.
6. The formulation as claimed in claim 5, wherein the said formulation is in the form of a combination tablet.

7. The formulation as claimed in claim 6, wherein the tablet is selected from ezetimibe 10mg and simvastatin 5mg.
8. The formulation as claimed in claim 6, wherein the tablet is selected from ezetimibe 10mg and simvastatin 10mg.
- 5 9. The formulation as claimed in claim 6, wherein the tablet is selected from ezetimibe 10mg and simvastatin 20mg.
- 10 10. The formulation as claimed in claim 6, wherein the tablet is selected from ezetimibe 10mg and simvastatin 40mg.
11. The formulation as claimed in claim 6, wherein the tablet is selected from ezetimibe 10mg and atorvastatin 5mg.
12. The formulation as claimed in claim 6, wherein the tablet is selected from ezetimibe 10mg and atorvastatin 10mg.
13. The formulation as claimed in claim 6, wherein the tablet is selected from ezetimibe 10mg and atorvastatin 20mg.
- 15 14. The formulation as claimed in claim 6, wherein the tablet is selected from ezetimibe 10mg and atorvastatin 40mg.
15. The formulation as claimed in claim 6, wherein the tablet is selected from ezetimibe 10mg and atorvastatin 80mg.
16. The formulation as claimed in claim 6, wherein the tablet is selected from ezetimibe 10mg and rosuvastatin 5mg.
- 20 17. The formulation as claimed in claim 6, wherein the tablet is selected from ezetimibe 10mg and rosuvastatin 10mg.
18. The formulation as claimed in claim 6, wherein the tablet is selected from ezetimibe 10mg and rosuvastatin 20mg.
- 25 19. The formulation as claimed in claim 1, wherein at least one additional excipient is used.
20. The formulation as claimed in claim 19, wherein the additional excipient is selected from pharmaceutical lubricants, disintegrators, binders, glidants, fillers or diluent and a mixture thereof
- 30 21. The formulation as claimed in claim 20, wherein the filler is selected from calcium carbonate, dibasic calcium phosphate, lactose, magnesium carbonate, sucrose, starch, magnesium oxide, lactose anhydrous, microcrystalline cellulose and mannitol; and a mixture thereof.

22. The formulation as claimed in claim 20, wherein the lubricant is selected from stearic acid, a salt of stearic acid, talc, sodium stearyl fumarate, glyceryl behenate, magnesium silicate, magnesium trisilicate and hydrogenated castor oil; and a mixture thereof.
- 5 23. The formulation as claimed in claim 20, wherein the disintegrator is selected from starch, sodium starch glycolate, croscarmellose sodium, crospovidone, carboxymethylcellulose calcium, carboxymethylcellulose sodium and magnesium aluminum silicate; and a mixture thereof.
- 10 24. The formulation as claimed in claim 20, wherein the glidant is selected from colloidal anhydrous silica and talc; and a mixture thereof.
25. The formulation as claimed in claim 20, wherein the binder is selected from hydroxypropyl cellulose, polyvinylpyrrolidone k-30, hydroxypropyl cellulose (low-substituted) and starch; and a mixture thereof.
- 15 26. The formulation as claimed in claim 1, wherein ezetimibe, simvastatin, starlac, ethanol, butylated hydroxy anisole, magnesium stearate, crospovidone, croscarmellose sodium, hydroxypropylcellulose (low-substituted) purified talc, lake brilliant blue, colloidal anhydrous silica, hydroxypropylmethylcellulose-15cps, titanium dioxide and triacetin.
- 20 27. The formulation as claimed in claim 26, wherein ezetimibe in the range of 1 to 10% by weight, simvastatin in the range of 2 to 23% by weight, starlac in the range of 41 to 97% by weight, butylated hydroxy anisole in the range of 0.01 to 0.004% by weight, magnesium stearate in the range of 1 to 3% by weight, crospovidone in the range of 1 to 6% by weight, croscarmellose sodium in the range of 1 to 4% by weight, hydroxypropylcellulose (low-substituted) in the range of 2 to 7% by weight, colloidal anhydrous silica in the range of 0.5 to 2% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps in the range of 37 to 89.5% by weight, purified talc in the range of 4 to 12% by weight, lake brilliant blue in the range of 4 to 14% by weight, titanium dioxide in the range of 7 to 18% by weight and triacetin in the range of 3 to 9% by weight, based on the total weight of the coating material.
- 25 30 28. The formulation as claimed in claim 27, wherein ezetimibe in the range of 1.5 to 7.5% by weight, simvastatin in the range of 3 to 18% by weight, starlac in the range of 61 to 87% by weight, butylated hydroxy anisole in

the range of 0.01 to 0.03% by weight, magnesium stearate in the range of 1.5 to 2.5% by weight, crospovidone in the range of 1.5 to 5% by weight, croscarmellose sodium in the range of 1.5 to 3% by weight, hydroxypropylcellulose (low-substituted) in the range of 2.5 to 6.5% by weight, colloidal anhydrous silica in the range of 0.5 to 1.5% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps in the range of 56 to 70% by weight, purified talc in the range of 7 to 9.5% by weight, lake brilliant blue in the range of 9 to 11% by weight, titanium dioxide in the range of 11 to 14.5% by weight and triacetin in the range of 5 to 6.5% by weight, based on the total weight of the coating material.

29. The formulation as claimed in claim 28, wherein ezetimibe is 6.7% by weight, simvastatin is 3.3% by weight, starlac is 77.3% by weight, butylated hydroxy anisole is 0.02% by weight, magnesium stearate is 1.7% by weight, crospovidone is 2.7% by weight, croscarmellose sodium is 2% by weight, hydroxypropylcellulose (low-substituted) is 5.3% by weight, colloidal anhydrous silica is 1% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps is 63.7% by weight, purified talc is 8% by weight, lake brilliant blue is 10% by weight, titanium dioxide is 12.7% by weight and triacetin is 5.7% by weight, based on the total weight of the coating material.

30. The formulation as claimed in claim 28, wherein ezetimibe is 5.6 % by weight, simvastatin is 5.6% by weight, starlac is 79.4% by weight, butylated hydroxy anisole is 0.02% by weight, magnesium stearate is 1.7% by weight, crospovidone is 2.2% by weight, croscarmellose sodium is 1.7% by weight, hydroxypropylcellulose (low-substituted) is 2.8% by weight, colloidal anhydrous silica is 1.1% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps is 63.6% by weight, purified talc is 8.1% by weight, lake brilliant blue is 10% by weight, titanium dioxide is 12.8% by weight and triacetin is 5.6% by weight, based on the total weight of the coating material.

31. The formulation as claimed in claim 28, wherein ezetimibe is 3.3% by weight, simvastatin is 6.7% by weight, starlac is 78.1% by weight, butylated hydroxy anisole is 0.03% by weight, magnesium stearate is 1.7%

- by weight, crospovidone is 2% by weight, croscarmellose sodium is 1.7% by weight, hydroxypropylcellulose (low-substituted) is 5.7% by weight, colloidal anhydrous silica is 0.8% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps is 63.5% by weight, purified talc is 8.2% by weight, lake brilliant blue is 10% by weight, titanium dioxide is 12.7% by weight and triacetin is 5.7% by weight, based on the total weight of the coating material.
- 5
32. The formulation as claimed in claim 28, wherein ezetimibe is 2.6% by weight, simvastatin is 10.3% by weight, starlac is 75.1% by weight, butylated hydroxy anisole is 0.02% by weight, magnesium stearate is 2.1% by weight, crospovidone is 2.1% by weight, croscarmellose sodium is 1.8% by weight, hydroxypropylcellulose (low-substituted) is 5.1% by weight, colloidal anhydrous silica is 1% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps is 63.2% by weight, purified talc is 8.2% by weight, lake brilliant blue is 10% by weight, titanium dioxide is 12.8% by weight and triacetin is 2.3% by weight, based on the total weight of the coating material.
- 10
- 15
33. The formulation as claimed in claim 28, wherein ezetimibe is 2% by weight, simvastatin is 16% by weight, starlac is 67.8% by weight, butylated hydroxy anisole is 0.02% by weight, magnesium stearate is 2% by weight, crospovidone is 4% by weight, croscarmellose sodium is 2.6% by weight, hydroxypropylcellulose (low-substituted) is 4.6% by weight, colloidal anhydrous silica is 1% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps is 63.3% by weight, purified talc is 8.1% by weight, lake brilliant blue is 10% by weight, titanium dioxide is 12.8% by weight and triacetin is 5.8% by weight, based on the total weight of the coating material.
- 20
- 25
34. The formulation as claimed in claim 1, wherein ezetimibe, atorvastatin and rosuvastatin or a salt thereof, light calcium carbonate, lactose, starch, croscarmellose sodium, polyvinylpyrrolidone k-30, isopropyl alcohol, magnesium stearate, purified talc, lake sunset yellow, colloidal anhydrous silica, crospovidone, hydroxypropylmethylcellulose-15cps, titanium dioxide and triacetin.
- 30

35. The formulation as claimed in claim 34, wherein ezetimibe in the range of 1.5 to 13% by weight, atorvastatin or a salt thereof in the range of 3 to 31% by weight, light calcium carbonate in the range of 2 to 8% by weight, lactose in the range of 27 to 80% by weight, starch in the range of 5 to 24% by weight, croscarmellose sodium in the range of 2 to 8% by weight, polyvinylpyrrolidone k-30 in the range of 1 to 7% by weight, magnesium stearate in the range of 1 to 4% by weight, colloidal anhydrous silica in the range of 0.5 to 2.5% by weight, crospovidone in the range of 1.5 to 6% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps in the range of 50 to 90% by weight, purified talc in the range of 5 to 10% by weight, lake sunset yellow in the range of 0.5 to 2% by weight, titanium dioxide in the range of 8.5 to 18% by weight and triacetin in the range of 4 to 8% by weight, based on the total weight of the coating material.
36. The formulation as claimed in claim 35, wherein ezetimibe in the range of 2 to 10% by weight, atorvastatin or a salt thereof in the range of 4 to 24% by weight equivalent to atorvastatin, light calcium carbonate in the range of 3 to 6.5% by weight, lactose in the range of 40 to 63% by weight, starch in the range of 8 to 19% by weight, croscarmellose sodium in the range of 3 to 6% by weight, polyvinylpyrrolidone k-30 in the range of 2.5 to 6% by weight, magnesium stearate in the range of 1.5 to 3% by weight, colloidal anhydrous silica in the range of 0.5 to 2% by weight, crospovidone in the range of 2 to 4.5% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps in the range of 65 to 80% by weight, purified talc in the range of 7 to 9% by weight, lake sunset yellow in the range of 1 to 1.5% by weight, titanium dioxide in the range of 11 to 14.5% by weight and triacetin in the range of 5 to 7% by weight, based on the total weight of the coating material.
37. The formulation as claimed in claim 36, wherein ezetimibe is 9.09% by weight, atorvastatin or a salt thereof is 4.92% by weight equivalent to atorvastatin, light calcium carbonate is 3.64% by weight, lactose is 51.4% by weight, starch is 17.3% by weight, croscarmellose sodium is 3.62% by weight, polyvinylpyrrolidone k-30 is 4.09% by weight, magnesium stearate is 1.82% by weight, colloidal anhydrous silica is 1.36% by weight,

crospovidone is 2.73% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps is 72.3% by weight, purified talc is 7.73% by weight, lake sunset yellow is 1.36% by weight, titanium dioxide is 12.7% by weight and triacetin is 5.91% by weight, based on the total weight of the coating material.

5 38. The formulation as claimed in claim 36, wherein ezetimibe is 6.7% by weight, atorvastatin or a salt thereof is 7.2% by weight equivalent to atorvastatin, light calcium carbonate is 4.7% by weight, lactose is 56.8% by weight, starch is 10.7% by weight, croscarmellose sodium is 3.4% by weight, polyvinylpyrrolidone k-30 is 5% by weight, magnesium stearate is 2% by weight, colloidal anhydrous silica is 1% by weight, crospovidone is 2.7% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps is 72.3% by weight, purified talc is 8% by weight, lake sunset yellow is 1.33% by weight, titanium dioxide is 12.7% by weight and triacetin is 5.7% by weight, based on the total weight of the coating material.

10 39. The formulation as claimed in claim 36, wherein ezetimibe is 5.56% by weight, atorvastatin or a salt thereof is 12% by weight equivalent to atorvastatin, light calcium carbonate is 5.56% by weight, lactose is 51.3% by weight, starch is 8.89% by weight, croscarmellose sodium is 4.6% by weight, polyvinylpyrrolidone k-30 is 3.33% by weight, magnesium stearate is 2.22% by weight, colloidal anhydrous silica is 1.7% by weight, crospovidone is 3.9% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps is 72.2% by weight, purified talc is 8.06% by weight, lake sunset yellow is 1.39% by weight, titanium dioxide is 12.8% by weight and triacetin is 5.56% by weight, based on the total weight of the coating material.

20 40. The formulation as claimed in claim 36, wherein ezetimibe is 3.3% by weight, atorvastatin or a salt thereof is 14.4% by weight equivalent to atorvastatin, light calcium carbonate is 5% by weight, lactose is 50.3% by weight, starch is 11.7% by weight, croscarmellose sodium is 4.4% by weight, polyvinylpyrrolidone k-30 is 2.8% by weight, magnesium stearate is 2.7% by weight, colloidal anhydrous silica 1.3% by weight, crospovidone is 4% by weight, based on the total weight of the tablet,

hydroxypropylmethylcellulose-15cps is 71.83% by weight, purified talc is 8.17% by weight, lake sunset yellow is 1.33% by weight, titanium dioxide is 12.8% by weight and triacetin is 5.83% by weight, based on the total weight of the coating material.

- 5 41. The formulation as claimed in claim 36, wherein ezetimibe is 2.56% by weight, atorvastatin or a salt thereof is 22.2% by weight equivalent to atorvastatin, light calcium carbonate is 5.13% by weight, lactose is 44.9% by weight, starch is 10.3% by weight, croscarmellose sodium is 4.6% by weight, polyvinylpyrrolidone k-30 is 2.82% by weight, magnesium stearate
10 is 2.31% by weight, colloidal anhydrous silica is 1.3% by weight, crospovidone is 3.9% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps is 71.8% by weight, purified talc is 8.21% by weight, lake sunset yellow is 1.41% by weight, titanium dioxide is 12.8% by weight and triacetin is 5.77% by weight, based on the total
15 weight of the coating material.
42. The formulation as claimed in claim 34, wherein ezetimibe in the range of 2 to 13% by weight, rosuvastatin; or a salt thereof in the range of 2 to 10.5% by weight equivalent to rosuvastatin, light calcium carbonate in the range of 1 to 4% by weight, lactose in the range of 32 to 83% by weight,
20 starch in the range of 8 to 21% by weight, croscarmellose sodium in the range of 2 to 6.5% by weight, polyvinylpyrrolidone k-30 in the range of 1 to 5% by weight, magnesium stearate in the range of 1 to 3.5% by weight, colloidal anhydrous silica in the range of 0.5 to 2% by weight, crospovidone in the range of 2 to 7% by weight, based on the total weight
25 of the tablet, hydroxypropylmethylcellulose-15cps in the range of 52 to 93% by weight, purified talc in the range of 5 to 10% by weight, lake sunset yellow in the range of 0.5 to 2.5% by weight, titanium dioxide in the range of 8 to 16% by weight and triacetin in the range of 4 to 8% by weight, based on the total weight of the coating material.
- 30 43. The formulation as claimed in claim 42, wherein ezetimibe in the range of 3 to 10% by weight, rosuvastatin; or a salt thereof in the range of 4 to 8.5% by weight equivalent to rosuvastatin, light calcium carbonate in the range of 1.5 to 3% by weight, lactose in the range of 49 to 65% by weight, starch in the range of 12 to 16.5% by weight, croscarmellose sodium in the range

- of 2.5 to 5% by weight, polyvinylpyrrolidone k-30 in the range of 2 to 3.5% by weight, magnesium stearate in the range of 1.5 to 3% by weight, colloidal anhydrous silica in the range of 0.5 to 1.5% by weight, crospovidone in the range of 4 to 5.5% by weight; based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps in the range of 65 to 80% by weight, purified talc in the range of 7 to 9% by weight, lake sunset yellow in the range of 1 to 2% by weight, titanium dioxide in the range of 11 to 14% by weight and triacetin in the range of 5 to 6.5% by weight, based on the total weight of the coating material.
- 5
- 10 44. The formulation as claimed in claim 43, wherein ezetimibe is 9.09% by weight, rosuvastatin or a salt thereof is 4.74% by weight equivalent to rosuvastatin, light calcium carbonate is 2.3% by weight, lactose is 54.5% by weight, starch is 13.9% by weight, croscarmellose sodium is 4.6% by weight, polyvinylpyrrolidone k-30 is 3.2% by weight, magnesium stearate is 1.8% by weight, colloidal anhydrous silica is 0.9% by weight, crospovidone is 5% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps is 71.8% by weight, purified talc is 8.2% by weight, lake sunset yellow is 1.4% by weight, titanium dioxide is 12.7% by weight and triacetin is 5.9% by weight, based on the total weight of the coating material.
- 15
- 20
- 25 45. The formulation as claimed in claim 43, wherein ezetimibe is 5.7% by weight, rosuvastatin or a salt thereof is 5.95% by weight equivalent to rosuvastatin, light calcium carbonate is 2.3% by weight, lactose is 57.5% by weight, starch is 13.7% by weight, croscarmellose sodium is 4% by weight, polyvinylpyrrolidone k-30 is 2.9% by weight, magnesium stearate is 2.3% by weight, colloidal anhydrous silica is 1.1% by weight, crospovidone is 4.6% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps is 72.3% by weight, purified talc is 8% by weight, lake sunset yellow is 1.43% by weight, titanium dioxide is 12.6% by weight and triacetin is 5.7% by weight, based on the total weight of the coating material.
- 30
46. The formulation as claimed in claim 43, wherein ezetimibe is 3.6% by weight, rosuvastatin or a salt thereof is 7.4% by weight equivalent to rosuvastatin, light calcium carbonate is 2.1% by weight, lactose is 58.8%

by weight, starch is 14.8% by weight, croscarmellose sodium is 3.2% by weight, polyvinylpyrrolidone k-30 is 2.3% by weight, magnesium stearate is 1.8% by weight, colloidal anhydrous silica is 0.9% by weight, crospovidone is 5% by weight, based on the total weight of the tablet, hydroxypropylmethylcellulose-15cps is 72.1% by weight, purified talc is 8.04% by weight, lake sunset yellow is 1.43% by weight, titanium dioxide is 12.7% by weight and triacetin is 5.7% by weight, based on the total weight of the coating material.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 2005/000196

A. CLASSIFICATION OF SUBJECT MATTER

IPC⁸: **A61K 31/397** (2006.01); **A61K 31/40** (2006.01); **A61K 31/66** (2006.01);
A61K 31/63 (2006.01); **A61K 9/20** (2006.01); **A61P 3/06** (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁸: A61K 31/00, A61K 9/20Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
----Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPI, Medline

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/0133011 A1 (WADDEL et al.) 8 July 2004 (08.07.2004) page 11, paragraphs [0228], [0238], page 12, paragraph [0252]. --	1, 2, 5-25
A	WO 2004/017896 A2 (MERCK & CO., INC.) 4 March 2004 (04.03.2004) claims 11, 12, 17, 18, 19. -----	1-46

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
28 February 2006 (28.02.2006)Date of mailing of the international search report
8 March 2006 (08.03.2006)Name and mailing address of the ISA/ AT
Austrian Patent Office
Dresdner Straße 87, A-1200 ViennaAuthorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter application No.
PCT/IN 2005/000196

Patent document cited in search report			Publication date	Patent family member(s)		Publication date	
A				none			
US	A	20040133011		none			
WO	A2	2004017896	2004-03-04	JP	T	2006500378T	2006-01-05
				EP	A2	1545540	2005-06-29
				CA	A1	2495799	2004-03-04
				AU	A1	2003256419	2004-03-11